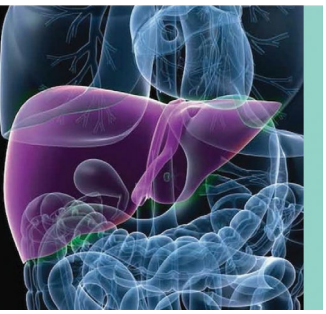

A History of the Assessment of Liver Performance

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Abbreviations: ALF, acute liver failure; BSP, bromsulphalein; CTP, Child-Turcotte-Pugh; HVPG, hepatic venous pressure gradient; ICG, indocyanine green; ICU, intensive care unit; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MELD, Mayo End-Stage Liver Disease Model (Model for End-Stage Liver Disease); MELD-Na, Model for End-Stage Liver Disease—Sodium; TIPS, transjugular intrahepatic portosystemic shunt.

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HISTORY FROM ANCIENT TO MODERN

In antiquity, inspection of the liver, *hepatoscopy* (*hēpatoskōpia*, from the Greek ηπατοσκόπια), was a common method among Babylonians, Etruscans, Greeks (Fig. 1), and Romans to use the liver to seek knowledge of the future using supernatural means,[1] but not for the purpose of assessing the performance of this *royal* organ. Ezekiel, the sixth century BCE biblical prophet who lived during the Babylonian captivity and had warned earlier about the impending destruction of Jerusalem, documented the popular Babylonian practice of *hepatomancy* (*ηπατομανία*) that is divination of the will of the gods via hepatoscopy of the livers of carefully selected sheep. In this context, the venerable prophet reported that "the king of Babylon (i.e., Nebuchadnezzar) has stood at the fork of the road, at the crossroad of the two ways, to perform divination, to shake out arrows, to inquire of the household gods, to inspect the liver. On its right lobe was the omen of Jerusalem…"[2] Hepatoscopy convention ordained that signs on the right side (later called the *pars familiaris*) of the liver that were deemed favorable, such as gallbladder swelling, paradoxically predicted success of the enemy when present on the left (*pars hostilis*) side.[1] Guided by the omens, Nebuchadnezzar went to Jerusalem and not Rabbah (modern Amman in Jordan), with devastating effect. How different might the Middle East have looked today had the configuration of that ovine liver been different? Was the clue a tight embedding of the gallbladder in the substance of the liver on the left or deep enclosure of the hepatic duct in the porta hepatis?[1] We can only speculate.

Since Paleolithic times, the liver was appreciated to be a highly vascular organ, as evidenced by the remarkable cave art of prehistoric hunters, found at Lascaux in Southern France.[3] Moreover, the liver was also long considered to be the source of blood—the basis of life itself—described by the most esteemed of all Roman physicians, Aelius (alternatively Claudius) Galen (c. 130-210 CE; Fig. 2) of Pergamon (modern-day Bergama, in Izmir Provence, Western Turkey), as the *sanguifactionis officina*,[4] "the factory of the blood," that is the site of *sanguification*. It is not surprising, therefore, that the liver was chosen for inspection as a natural consequence of the deep-grounded belief that the soul, which was the jurisdiction of priests in those civilizations, resided there along with the source of emotions, feelings and desires, and even sexual potency. Later, of course, the heart usurped the liver's claim as the seat of the soul.[1] A Babylonian priest, known as a *Bārû*, was trained to recognize the predictive signs in the liver, and thus was collected a mountain of omens called the *Bārûtu*. These priests recognized that livers from similar animals never looked alike, which in Mesopotamia led to the use of clay liver models,[5] examples of which are

FIG 1 Greek inspection of the liver, depicted on a big-bellied amphora decorated with red figures by the Kleophrades Painter (510-470 BCE). Müler K. 1967 Die Leberschau in der Antike. Deutsche Laevosan-Gesellschaft, Mannheim.

FIG 2 Galen of Pergamon. Lithograph by Pierre Roche Vigneron.

held in the Middle East Department of the British Museum (Fig. 3) and date back to the Temple of Marduk in Babylon in 2000 BCE, in the age of Hammurabi (perhaps better written phonetically as *Hammurapi*[6]). These historic details were revealed in a trove of some 800 fragments of medical texts out of tens of thousands of potsherds excavated at Mound Kouyunjik, opposite the site of ancient Nineveh (modern Mosul), among the vast library of King Ashurbanapal of Assyria (668-626 BCE).[6] A clay model of an ox liver, dating from the 15th century BCE, was also found at the archeological site of Tel Hazor in the Upper Galilee, Israel, at the site of the Middle Bronze Age fortified city of Hazor.[7] Subsequently, durable Etruscan bronze models were produced (Fig. 4),[8] in which inscriptions on the liver surface showed divisions into regions assigned to specific deities of the Etruscan religion.

In the Etruscan tradition that was practiced in Ancient Rome (and which even persisted to the Middle Ages[9]), divination was performed by a *haruspex* (Fig. 1), who was trained to look for omens by performing *haruspicy*, from the Latin *haruspicina* meaning "inspecting entrails," and especially the livers, of sacrificed animals (after the archaic word *haru* and the root *spec*, "to observe"). Perhaps the most famous haruspex in ancient Rome was the soothsayer Spurinna, at whose warnings about the Ides of March* Julius Caesar scoffed to his cost, at least according to Suetonius.[10] Haruspicy contrasts with divination performed by an augur, who interprets the will of the gods by "taking the auspices," that is, studying the flight of birds.

It was not until the Renaissance dawned, 1000 years after the fall of Rome, that there was any advance in understanding the anatomy and function of the liver. Throughout the Dark Ages and even in the latter part of the Middle Ages, the spiritual soul was more important than the physical body. Leonardo da Vinci (1452-1519) studied the anatomy of the human liver thoroughly[11] (Fig. 5), and apparently he even described different liver diseases, including cirrhosis, but his work in hepatology was relatively unknown until the latter half of the 18th century. Andreas Vesalius (1514-1564) mistakenly portrayed the liver as having five lobes in his famed anatomical drawings (*Tabulae Anatomicae Sex, Venice 1538*) based on his earlier dissection of a baboon (Fig. 6A), but he later derided that representation in his 1543 *De Humani Corporis Fabrica Septum* and accurately described the anatomy of the human liver and biliary tree in detail[12] (Fig. 6B), while yet perpetuating his errors of its portal venous anatomy.[13] He may have even found a correlation between excessive alcohol consumption and cirrhosis.[14] Galen and his adherents believed that the major function of liver was to convert digested food from the intestines into blood by *concoction* (*pepsis*) and to separate the light (yellow) bile for excretion via the biliary tree from the heavy (black) bile that would pass via the spleen to the stomach. Yet, even up to the late Middle Ages, there was still no inkling that the liver had any function other than bile production.[15] Several centuries elapsed before the celebration of the liver by Dutch anatomist Thomas Bartholin,† as "the body's master cook and engineer" that "cooks and stews for us…"[16]

In 1654, Francis Glisson (1597-1677 CE), a young colleague of William Harvey and a founder of both the Royal Society (of Great Britain) and the Royal College of

**Et immolantem haruspex Spurinna monuit, caveret periculum, quod non ultra Martias Idus proferretur.* "Again, when he was offering sacrifices, the soothsayer Spurinna warned him to beware of danger, which would come not later than the Ides of March." (*De Vitis Caesarum, Divus Iulius* ch. LXXXI).

†As expressed in his Latin dirge on the death of the liver, which was published in 1653: Bartholinus T. *Vasa lymphatica, nuper Hafniae in animalibus inventa et hepatis exsequiae.* Paris.

FIG 3 Clay model of sheep liver held at the Middle East Department of the British Museum, London. This teaching model dates from 1900-1600 BCE, probably from the ancient Sumerian/Babylonian city of Sippar, 30 km southwest of modern Baghdad. The surface is divided into boxes in which are described the implications of blemishes found in this region of the sacrificed sheep's liver; wooden pegs were inserted into the holes to record the blemishes that were found, for later divination. Reproduced with permission. © Board of Trustees at the Middle East Department of the British Museum, London.

FIG 4 The famous Bronze Liver (Iecur Placentinum) of Piacenza is held in the Musei Civici Di Palazzo Farnese, Piacenza, Italy. This teaching model or memory aid that dates from the early second/late first century BCE Etruscan period was found in 1877 by a peasant working in his field, in nearby Decima di Gossolengo, presumably having been lost there by a haruspex during the 80s BCE civil wars of Lucius Cornelius Sulla. The inscriptions on the surface of the liver (below right) indicate the domains of the Etruscan gods. Photograph reproduced with permission from Musei Civici Di Palazzo Farnese, Piacenza, Italy.

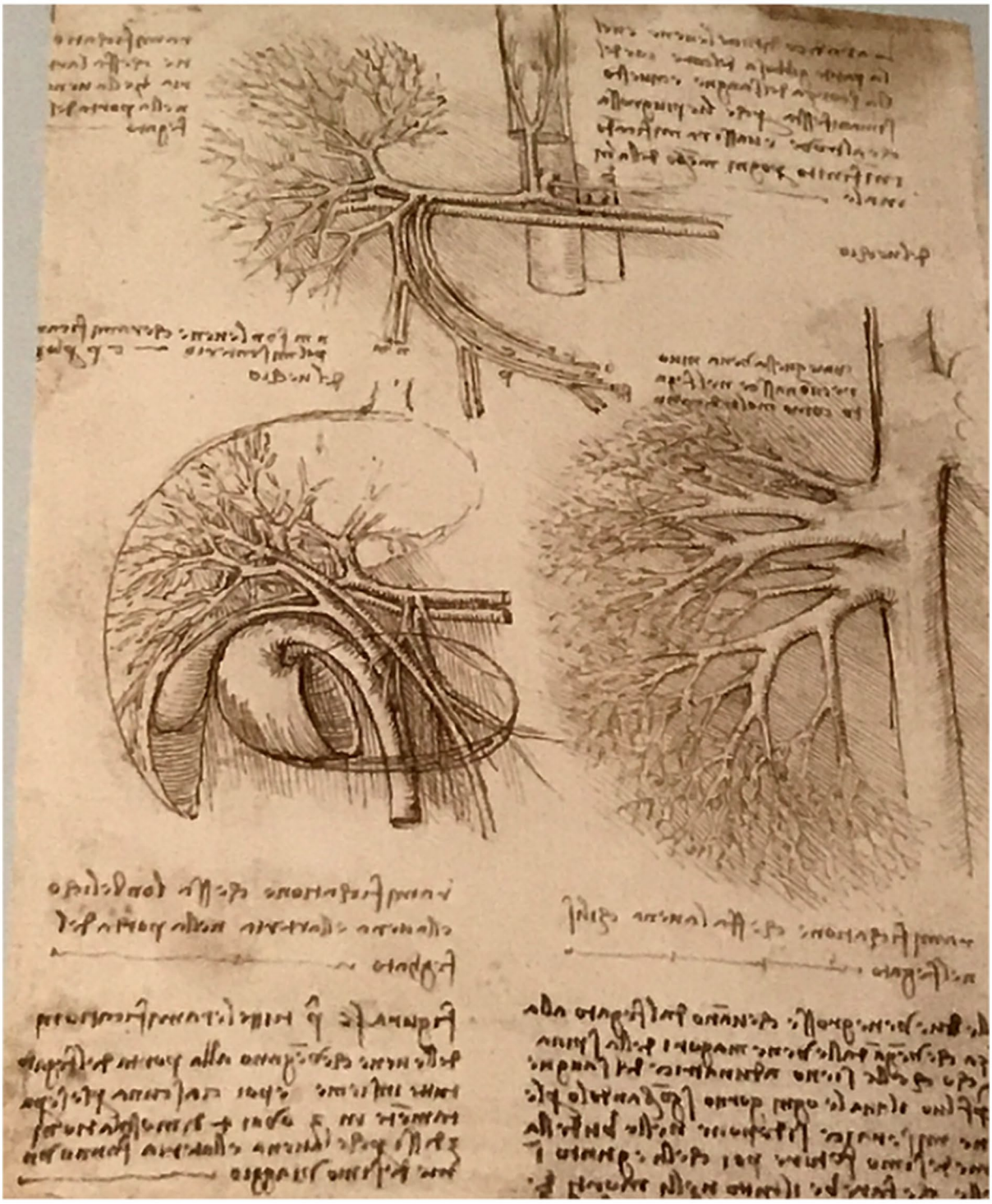


FIG 5 "The Vessels of the Liver" by Leonardo da Vinci in Dell'Anatomia Fogli B circa 1508. From the Leonardo da Vinci Anatomical Drawings Collection held in the Royal Library, Windsor Castle. RCIN 91905v, Royal Collection Trust/© Her Majesty Queen Elizabeth II 2018. (Top) Intrahepatic branches of the hepatic artery and portal vein. (Bottom left) Branches of the umbilical vein, portal vein, hepatic artery, and bile duct, with both the gallbladder and bile duct. (Bottom right) The hepatic veins and their junction with the inferior vena cava. See Video 1 (watch here), a video animation of liver blood flow, as portrayed in a drawing by Leonardo Da Vinci and devised by the renowned British heart surgeon Francis Wells, Royal Collection Press Office. Reprinted with permission from © ATS Heritage.

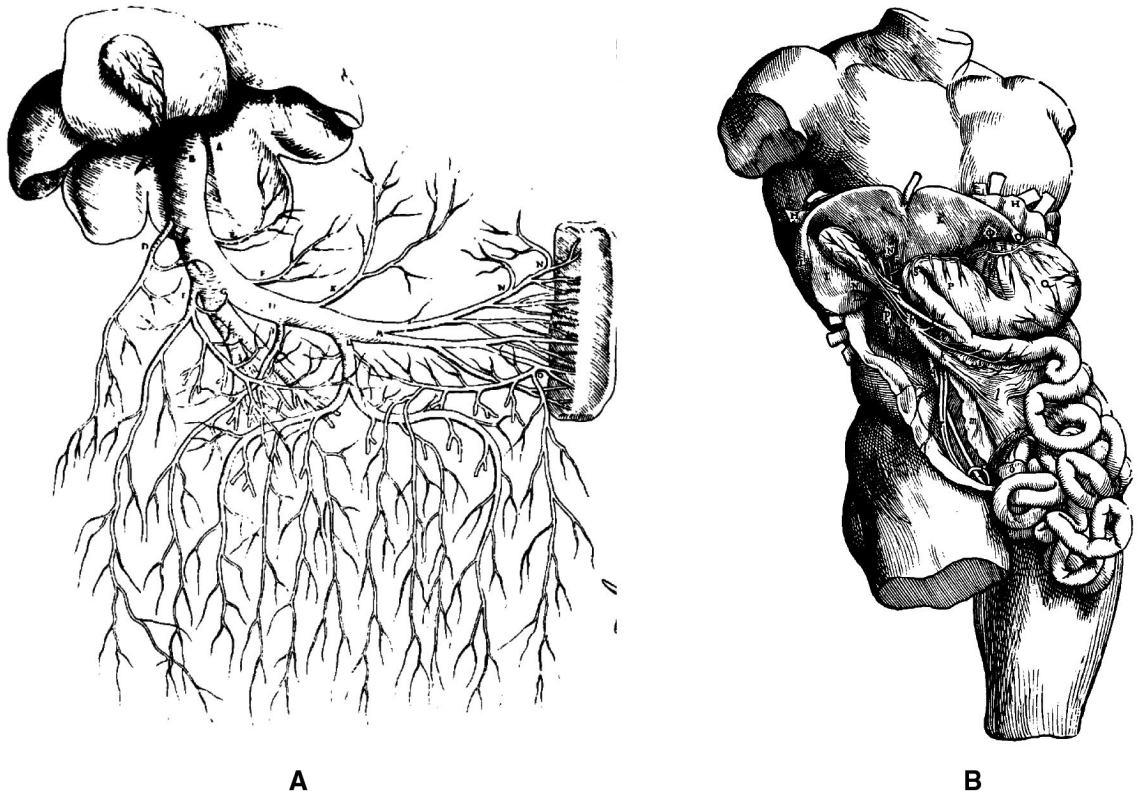


FIG 6 Liver illustrations by Andreas Vesalius (A) from *Tabulae Anatomicae Sex, Venice (1538)* showing a five-lobed liver and (B) from *De Humani Corporis Fabrica Libri Septum*, *Basel (1543)* showing a two-lobed liver reflected upward to display its visceral surface.

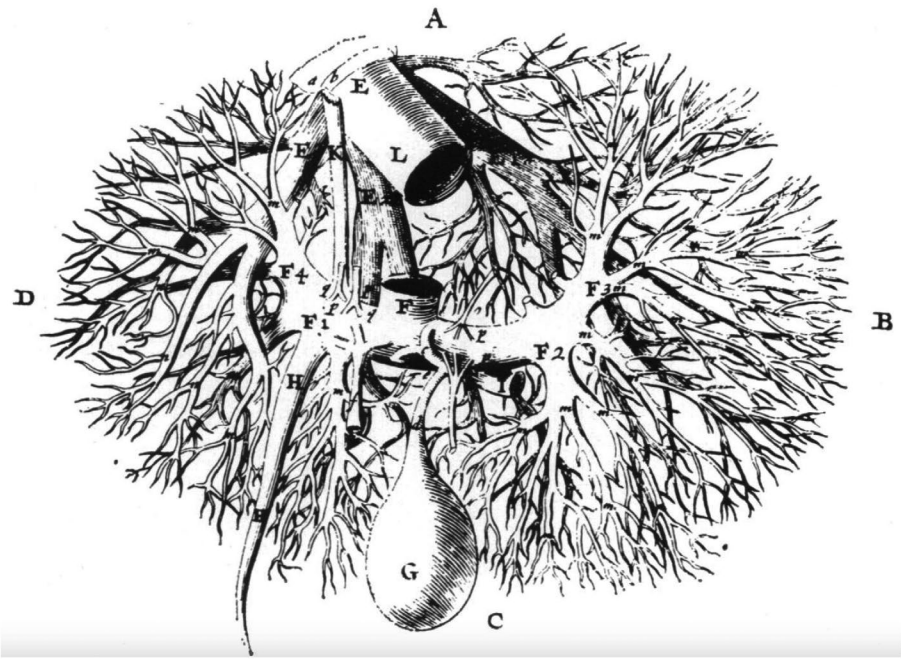


FIG 7 One of Glisson's drawings of a cast of the intrahepatic vessels, from his *Anatomia Hepatis.* London: Typis Du-Gardiani; 1654.[17]

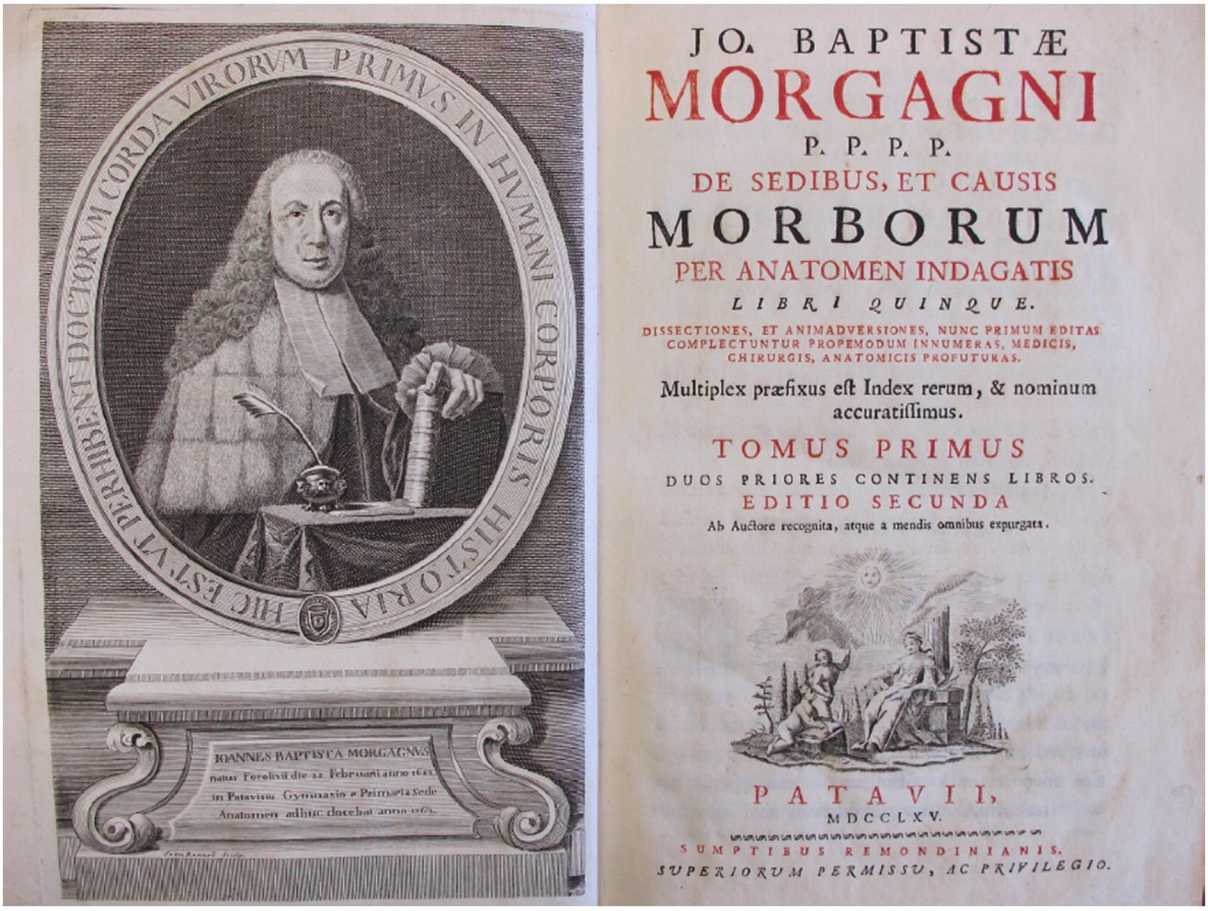


FIG 8 Title page of the 1765 second edition of Morgagni's *De sedibus et causis morborum per anatomen indagatis.*

Physicians, London, declared in his authoritative monograph on the liver that the hepatic parenchyma was responsible for the liver's function,[17] namely, the separation of bile from the blood by the mechanisms of so-called affinity. A finding published in 1666 by Marcello Malpighi (1628-1694),[18] using primitive microscopy, albeit antedated a couple of years earlier by Johan Jacob Wepfer,[19] that the parenchyma was arranged into grape-like outbudding structures that he termed *lobules*, comprising *lobuli* and *glandulosi acini*, convinced him that there had to be a functional connection between the hepatic parenchyma and adjacent vascular structures. The architecture of the hepatic lobule in humans was elegantly demonstrated by Kiernan in 1833 using only a hand lens.[20]

There are intriguing links between the appreciation of liver function and Glisson's pivotal demonstration of intravascular channels in the liver[21] (Fig. 7), which he proved by injecting "warm water, coloured with a little milk" into the portal vein of a fresh human cadaver, using an ox bladder attached to a siphon (such as was used for administrating enemas). With the result of this perfusion experiment, Glisson vindicated the renowned physician-anatomist, Erasistratus of Chios (310-250 BCE),[22] who postulated the existence of intrahepatic vascular channels and who had actually coined the term *parenchyma* (παρέγχυμα, meaning "adjoining infusion") that in Glisson's mind was the locus of the liver's function. It is likely that, in common with Glisson, Erasistratus considered that in anatomy, as in architecture, "Form follows function," thereby presciently espousing the 1896 views of the renowned Chicago architect Louis Sullivan (1856-1924) that the latter published over the course of 1901 as his *Kindergarten Chats* in the *Interstate Architect and Builder*.[‡] Or, as Sullivan's most distinguished apprentice, Frank Lloyd Wright (1867-1959), later paraphrased in his *Dear Master's* ordinance, "Form and function are one."[23] Galen did not ignore the

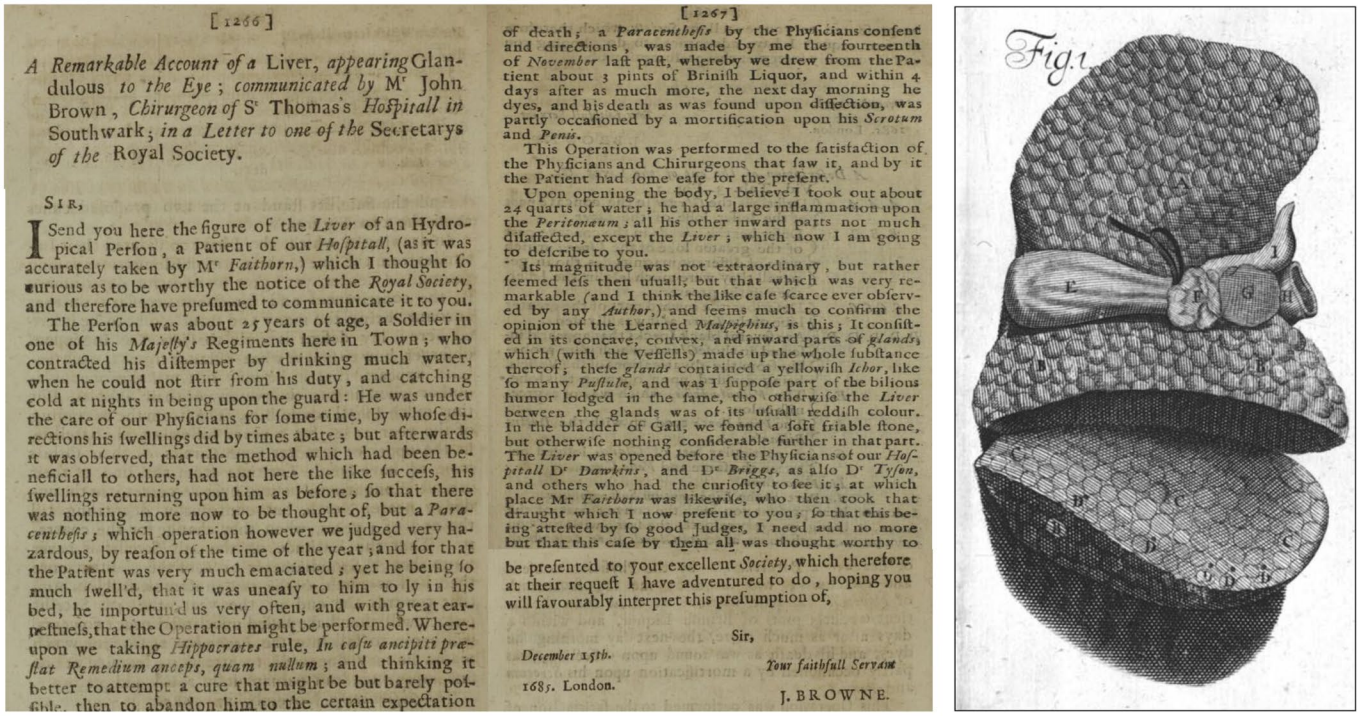
[‡]These essays were not published in book form until 1934, a decade after Sullivan's death.

impressive body of anatomical discoveries of his Alexandrian predecessor, but he was bitterly critical of the latter's inference about an organ's function, based on its anatomy. Incidentally, Francis Glisson's experiment also provided crucial evidence for the hypothesis by that Man of Kent from Folkestone, United Kingdom, William Harvey (1578-1657 CE),[24] that blood flows through the lungs, because the milky water he injected into the portal vein passed sequentially through the right heart, the lungs, and the left heart into the systemic arterial circulation. It was reasoned that if blood could pass through a dense organ like the liver from the portal vein to the vena cava seemingly without any propulsive force, then blood could surely flow through the delicate spongy lungs driven by the contraction of the heart's right ventricle.

Cirrhosis was described in detail from the 17th century onward, although the notion that a "hard" liver was a bad sign, especially in association with jaundice, can be traced back to Greek and Roman medicine from Hippocrates[25] and Aulus Cornelius Celsus[26] to Aretæeus the Cappadocian[27] and Caelius Aurelianus,[28] over a span of almost 1000 years (from 400 BCE though 500 CE). However, the terminology was not always unequivocally lucid, making interpretation of early clinicopathological entities difficult. Swelling that probably meant inflammation (i.e., hepatitis) was thought to progress to *hardness*, which we presume to equate with cirrhosis, and then to a *scirrhus* state that we interpret as carcinoma. Confusion was compounded by the widespread application of the label *tubercle* that was introduced by Giovanni Battista Morgagni (1682-1771) in his 1761 seminal mechanistic book, *De sedibus et causis morborum per anatomen indagatis* (Fig. 8)[29], to refer to *any* discrete liver mass that George Budd later referred to as nodules, often the size of peas, while scarring gave the surface of the liver a "hob-nailed appearance."[31] In the years before Laennec and Budd, livers were described as being *tubercular* and even *tuberculated*, despite there being no hint of tuberculosis. Further, Morgagni's failure to distinguish between cirrhosis and carcinoma[30] only contributes more uncertainty.

St Thomas's Hospital London surgeon John Browne (1642-1702) has long been credited with being the first to publish an illustration of a cirrhotic liver[32] (Fig. 9) that was drawn by the distinguished crayon artist and engraver William Faithorne the Elder,[§] from an autopsy that

[§]During the English Civil War, Faithorne was imprisoned as a monarchist and briefly exiled to France.



[1266]

A Remarkable Account of a Liver, *appearing* Glandulous *to the Eye; communicated by* Mr John Brown, *Chirurgeon of* St Thomas's *Hospitall in* Southwark; *in a Letter to one of the* Secretarys *of the* Royal Society.

SIR,

I Send you here the figure of the *Liver* of an Hydropical Person, a Patient of our *Hospitall*, (as it was accurately taken by Mr *Faithorn*,) which I thought so curious as to be worthy the notice of the *Royal Society*, and therefore have presumed to communicate it to you.

The Person was about 25 years of age, a Soldier in one of his *Majesty's* Regiments here in Town; who contracted his distemper by drinking much water, when he could not stirr from his duty, and catching cold at nights in being upon the guard: He was under the care of our Physicians for some time, by whose directions his swellings did by times abate; but afterwards it was observed, that the method which had been beneficiall to others, had not here the like success, his swellings returning upon him as before; so that there was nothing more now to be thought of, but a *Paracenthesis*; which operation however we judged very hazardous, by reason of the time of the year; and for that the Patient was very much emaciated; yet he being so much swell'd, that it was uneasy to him to ly in his bed, he importun'd us very often, and with great earnestness, that the Operation might be performed. Whereupon we taking *Hippocrates* rule, *In casu ancipiti præstat Remedium anceps, quam nullum*; and thinking it better to attempt a cure that might be but barely possible, then to abandon him to the certain expectation

[1267]

of death; a *Paracenthesis* by the Physicians consent and directions, was made by me the fourteenth of *November* last past, whereby we drew from the Patient about 3 pints of Brinish Liquor, and within 4 days after as much more, the next day morning he dyes, and his death as was found upon dissection, was partly occasioned by a mortification upon his *Scrotum* and *Penis*.

This Operation was performed to the satisfaction of the Physicians and Chirurgeons that saw it, and by it the Patient had some ease for the present.

Upon opening the body, I believe I took out about 24 quarts of water; he had a large inflammation upon the *Peritonæum*; all his other inward parts not much disaffected, except the *Liver*; which now I am going to describe to you.

Its magnitude was not extraordinary, but rather seemed less then usuall; but that which was very remarkable (and I think the like case scarce ever observed by any *Author*,) and seems much to confirm the opinion of the Learned *Malpighius*, is this; It consisted in its concave, convex, and inward parts of *glands*, which (with the Vessells) made up the whole substance thereof; these *glands* contained a yellowish *Ichor*, like so many *Pustules*, and was I suppose part of the bilious humor lodged in the same, tho otherwise the *Liver* between the glands was of its usuall reddish colour. In the bladder of Gall, we found a soft friable stone, but otherwise nothing considerable further in that part. The *Liver* was opened before the Physicians of our *Hospitall* Dr *Dawkins*, and Dr *Brigge*, as also Dr *Tyson*, and others who had the curiosity to see it; at which place Mr *Faithorn* was likewise, who then took that draught which I now present to you; so that this being attested by so good Judges, I need add no more but that this case by them all was thought worthy to be presented to your excellent *Society*, which therefore at their request I have adventured to do, hoping you will favourably interpret this presumption of,

Sir,

December 15th. 1685. London.

Your faithfull Servant

J. BROWNE.

FIG 9 John Browne's illustration of a *glandulous-appearing* (i.e., cirrhotic) liver.[32] Key: (A) left lobe; (B) concave part of the right lobe; (C) cut surface of the right lobe; (D) black spots, possibly representing divided vessels; (E) gallbladder; (F) portal vein together with the bile duct; (G) liver tissue lying between the vena cava and the portal vein and bile duct; (H) vena cava.

the artist witnessed and was carried out by Browne himself. Although Browne attended both Charles II and his nephew William III (of Orange), and had an impressive list of innovations and achievements, it is sad to report that his reputation was stigmatized by brazenly copying from others, an apparently common practice in his time that was called piracy but which now would be plagiarism, an act that was not yet illegal in those days.[33] Matthew Baillie (1761-1823),[34] a Scottish physician, nephew of William and John Hunter (from each of whom he inherited a substantial museum of pathological specimens) and Physician in Ordinary to George III, was credited with having published the first systematic study of pathology and the first publication in English on pathology as a separate subject.[35] Oddly enough, he did not publish the accompanying illustrations from his own specimens and those from his uncles' considerable inheritance until much later, in a separate volume.[36] His description of cirrhosis is vivid, graphic, and almost lyrical,[37] but the name he chose for this pathological entity, namely, *Common tubercle of the liver* (Fig. 10), is a startling throwback to Morgagni. *Tubercles* of the liver include ordinary cirrhotic nodules, presumed neoplasms, and lesions related to scrofula or syphilitic gumma, and these Baillie carefully distinguished from tubercles that were "commonly produced by a long habit of drinking spirituous liquors."[37] Most notable, Baillie had recognized an association between drinking alcohol and liver disease.

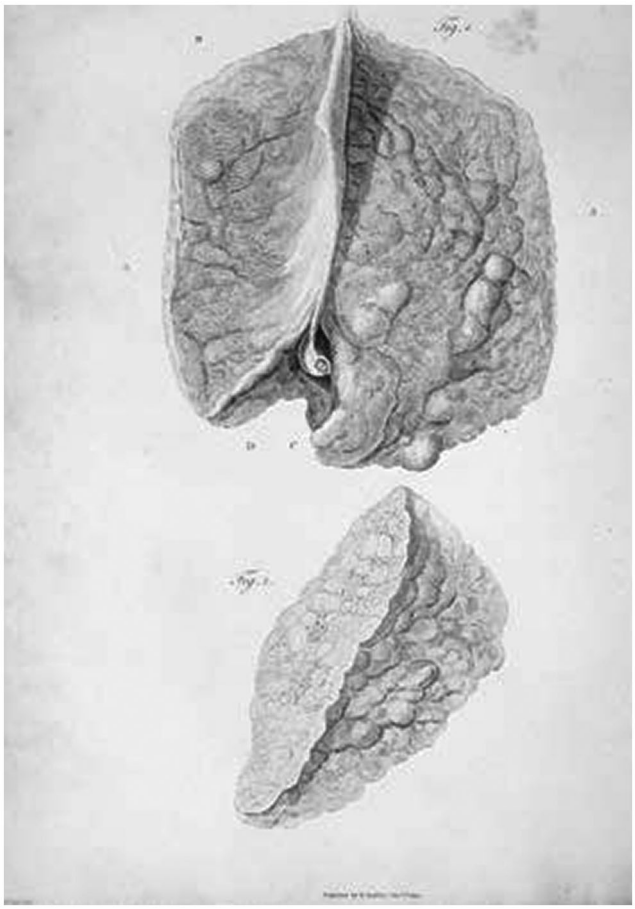


FIG 10 Matthew Baillie's illustration of a cirrhotic liver. From *A series of engravings accompanied with explanations which are intended to illustrate the morbid anatomy of some of the most important parts of the human body,*[36] Fascicle 5, Plate II. Portion of the external surface (top) and cross section (bottom) of the liver studded with tubercles. Line drawings by William Clift (John Hunter's former assistant), and engraving by James Basire.

Since the opportunity to give this multifaceted clinicopathological entity an enduring name was passed up by liver luminaries from antiquity to Browne and Baillie, the nomenclator's baton was taken up 25 years later by a tuberculous Parisian physician from Normandy,[38] who delighted in Latin and Greek. In what must surely be the all-time most celebrated footnote[39] in the History of Hepatology, René Theophile Hyacinthe Laennec (1781-1826), who had invented the stethoscope and made major contributions to the pathological understanding and diagnosis of diseases of the chest, coined the neologism "cirrhosis" that as a devoted classicist he derived from the Greek *kirrhos* (κιρρός), meaning "tawny yellow." The orange-yellow color referred to the appearance of the nodules in the diseased liver of the patient (whose pleurisy was the main focus of the famous 1819 case report), which he had in fact already described in a little known 16-page essay on *Les Cirrhoses* that was part of his incomplete *Treatise on Pathological Anatomy* (1804-1808) from 15 years earlier.[38] Whether the Laennec eponym that is popular in the United States, less so in Great Britain, and hardly at all in France is deserved for *alcoholic* cirrhosis, the memory of Laennec will surely prevail for devising the generic nomenclature itself, *cirrhosis*, for the clinicopathological entity that pervades our chosen field. It should come as no surprise that Laennec's moniker was not universally applauded; none other than Baron Carl (Freiherr) von Rokitansky (1804-1878), the renowned Bohemian Viennese pathologist, humanist philosopher, and liberal politician, preferred terms like *granular atropy* (*atrophie* in German) and *tuberculization*.[40] Parenthetically, in a later edition of *Traite de l'Auscultation*, Laennec cautions that the nodules of cirrhosis may be mistaken for malignant tumors (*squirrhe* in French).

Jaundice, the yellowing of the eyes, skin, mucous membranes and secretions, was perhaps the earliest appreciated expression of liver dysfunction to be recognized in all ancient systems of medicine—in the clay tablets of Mesopotamia, repeatedly in The Old Testament and Talmud,[41] in exquisite detail in the *Hippocratic Corpus*,[42] and in Ayurvedic[43] and Chinese[44] sources, where a plethora of traditional remedies were offered. Thus was created the need for one of the foremost early tests of liver function, which survives to this day. Once it had been determined that the function of the liver parenchyma was bile formation, the liver dysfunction responsible for jaundice (otherwise named *morbus regius* by Celsus[45] because of its gold color, or perhaps because of cure by the touch of a king or because only a king could afford its costly therapy) was deduced by Erasistratus to be due to impaired bile secretion. Yet in *Letter 37* in the 1769 edition of *The seats and causes of diseases, investigated by anatomy*…, Morgagni attributed jaundice to constriction of the liver by hepatic nerves caused by passion or emotional disturbance, for which Celsus some 1800 years previously had already recommended rest in a "good bed in a tasteful room" and emotional support.[45]

Encephalopathy and ascites also featured prominently in times of yore as manifestations of chronic liver dysfunction and, even now, together with jaundice, are included in a time-honored index that purports to assess liver performance.[46] For the first, we must distinguish the sudden delirium of acute liver injury, which had been observed and described by Hippocrates, Celsus, Galen, and their successors, in which there is fairly abrupt impairment or loss of true liver function, that is, the syndrome of acute liver failure (ALF; also known as fulminant hepatic failure)—as reviewed elegantly elsewhere in this series by Will Bernal and the late Roger Willims[47]—from the neuropsychiatric syndromes of disturbed behavior and reduced consciousness associated with portosystemic shunting in cirrhosis, that is, portosystemic encephalopathy. The History of Encephalopathy is the subject of a lively forthcoming essay in this series by Nathan Bass.

The challenge of ascites to the well-being of the individual was appreciated by the ancient Egyptians, the Hebrews, the Greeks, and the Mayans (Fig. 11) alike.[48] Hippocrates observed pithily that "when the belly becomes full of water, death follows."[49] Methods were devised early on to alleviate ascites, including physical drainage and the early

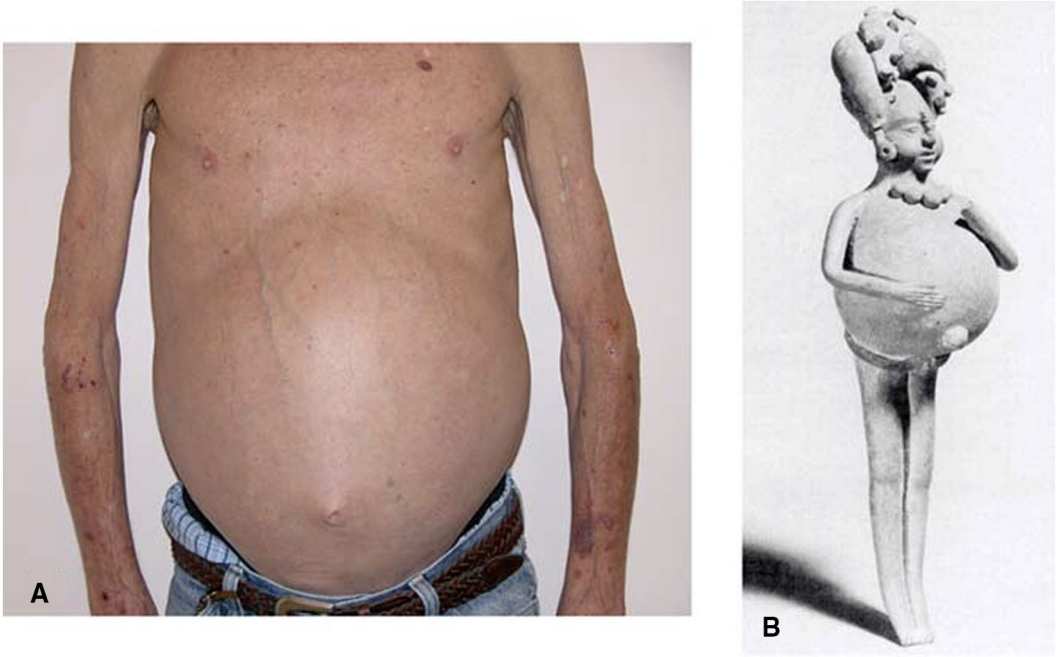


FIG 11 (A) Abdominal distension caused by ascites, showing an everted umbilicus and fine dilated superficial abdominal wall paraumbilical veins in which cephalad flow can be demonstrated by expelling blood between two fingers and observing the direction of return. Photograph provided by Dr. A. Reuben, Series Editor (B) Figurine from the Mayan burial site on the Island of Jaina (off the Yucatan Peninsula) depicting a man with massive ascites and eversion of the umbilicus. The Mayans of the classic period (300-900 CE) were familiar with the physical signs of massive ascites.[101] Reproduced with permission from *Annals of Internal Medicine*. Copyright 1994, Annual College of Physicians.

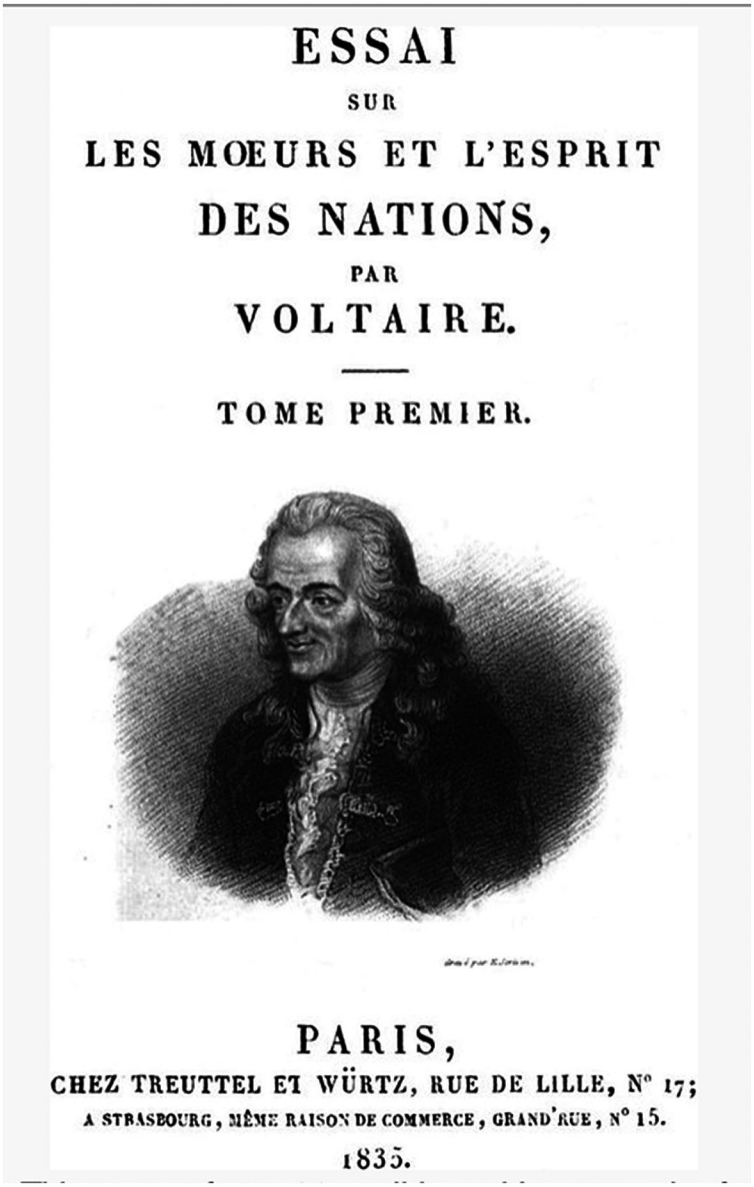

ESSAI
SUR
LES MŒURS ET L'ESPRIT
DES NATIONS,
PAR
VOLTAIRE.
TOME PREMIER.
PARIS,
CHEZ TREUTTEL ET WÜRTZ, RUE DE LILLE, N° 17;
A STRASBOURG, MÊME RAISON DE COMMERCE, GRAND'RUE, N° 15.
1835.

FIG 12 Title page of an 1835 edition of Voltaire's *Essai sur les mœurs et l'esprit des nations*, with a portrait of the author.

introduction of dietary salt restriction. The obvious expeditious remedy for massive ascites was to drain the offending fluid rapidly by tapping the barrel-shaped distended abdomen—a practice that Celsus favored and for which he even designed a lead or bronze tube with a retaining collar.[49] Erasistratus cautioned against rapid paracentesis, which he had abandoned in favor of opening the abdomen and inserting a catheter[50] (in his hands an implement shaped like a Roman S), as had been performed since the Hippocratists. Adherence to Erasistratus's counsel against the rapid removal of ascites (which Paul of Ægena thought would prove immediately fatal because it also "evacuates the vital spirit"[51]) persisted until the group in Barcelona documented that it is safe when performed in conjunction with intravenous (IV) albumin as a plasma expander.[52] As far back as Erasistratus, paracentesis was usually effected via the umbilicus (as described by Ambroise Paré[53]), but this site would scarcely be countenanced nowadays,[54] because of the risks for permanent leakage from the hernia sac and of puncture of portal hypertensive collateral veins (varices) even in the absence of a visible caput Medusa.

In the 18th and 19th centuries, additional observations were made in hepatobiliary disease regarding gallstones, liver tumors, fatty liver, hepatic congestion, and acute

hepatic necrosis; coincidentally, several formidable tomes (now of historic hepatological interest) devoted exclusively to liver disease were published by William Saunders,[55] George Budd,[31] Friedrich Theodor von Frerichs,[56] and Charles Murchison.[57] The 20th century was the beginning of the modern era of hepatology, spurred on by the exponential progress in the physical and biological sciences, epidemiology, immunology, microbial discovery, pathology, and light and electron microscopy. Among a plethora of anatomic features studied were the lobules of the human liver and its microcirculatory units,[58] along with a host of physiological, pathophysiological, and biochemical functions for which tests had already been devised in the early decades of the century,[59] including heme catabolism to bilirubin; bile composition and function; glycogenesis, gluconeogenesis, and other facets of carbohydrate metabolism; urea synthesis as the end stage of protein metabolism; detoxification processes; and aspects of deranged hepatic lipid metabolism that underlie microvesicular and macrovesicular fatty degeneration. Many scientists, in the tradition of Hippocrates and Galen, reported on jaundice caused by biliary obstruction, the infective hepatitides,[I] and other causes of dysregulated bilirubin metabolism and transport. Autoimmune hepatitis and primary biliary cirrhosis (later updated to primary biliary cholangitis) were recognized, and hemochromatosis and Wilson disease were differentiated from other causes of liver disease.[¶] Compared with these sublime scientific pursuits, clinical interest in "tight-lace" or "corset" liver, as a consequence of the capricious fashion of wearing barbarously rigid corsets to achieve an hourglass waist,[60] now appears almost comical. Yet an unexpected benefit of the end of the First World War, namely, the welcome demise of this misogynistic torture, is ostensibly not yet complete.[61-63]

The recognition of different classes and etiologies of liver disease, their influence on patient morbidity and mortality, and the development of medical and surgical therapies demanded the introduction of techniques not only for diagnosis but also for assessment of disease severity, as judged by the impairment of overall liver performance and ultimately its impact on prognosis. The early decades of the 20th century witnessed the development of a serum bilirubin test,[64] utilization of Bauer's 1906 galactose test,[65] hippuric acid synthesis assays[66] based on the research of Armand J. Quick (of Quick Test fame[67]), and tests based on the disposal by the body of a rainbow of dyes: indigo carmine, Congo red, methylene blue, Evans blue, Rose Bengal, indocyanine green (ICG), and arguably the most popular, the now-obsolete bromsulphalein (BSP) that is gloriously purple in alkaline solution. The clinical importance of the 1913 van den Bergh reaction for bilirubin estimation in the blood[64] was endorsed by many clinicians.[68] Serum bilirubin measurement subsequently became an important tool for distinguishing the different causes of scleral *icterus*—the equivalent Greek term for the Latin/French descriptor *jaundice* that refers to the yellow discoloration of the sclera, mucous membranes, the skin, and even cerebrospinal fluid—that Galen inferred as being either obstructive, concomitant, or hemolytic.[15] This included the detection of latent jaundice,[68] meaning an elevation of serum bilirubin below a level of ~3 mg/dL that should be evident on careful clinical inspection in a good light. The linguistic origins of both jaundice and icterus are discussed elsewhere in this series, as well as the ancient Greek and Jewish beliefs that placing a golden thrush or pigeon near the umbilicus would cure jaundice/icterus[69]—a practice that was fatal to the bird and that Celsus might have considered to be "complementary and alternative medicine."

It was not until the 1950s that the diagnostic value of the serum transaminases (officially referred to as aminotransferases since 1961[70]) was appreciated in the diagnosis of viral hepatitis.[71] There are many clinical applications for liver-associated serum biochemical tests that include aminotransferases, bilirubin, alkaline phosphatase, and albumin,[72] which are usually bundled together with the Quick prothrombin time (i.e., the number of seconds that it takes plasma to clot in a test tube)—a major facet of blood coagulation in which the liver has a near monopoly.[67] Such blood test bundles are popularly but, as Gerald Klatskin pointed out in 1948,[73] erroneously denoted as "liver function tests" (LFTs), yet they are widely used essential noninvasive tools of hepatology. It is not commonly known that the term *liver function test* had been in use since the 1930s[59] at least and included some curious laboratory procedures that are reminiscent of alchemy and witchcraft, in which the flocculation of negatively charged colloids of gold by serum globulin or the precipitation of gammaglobulins from serum by heavy metals, pungent phenols, or mixtures of sheep brain cephalin and cholesterol was relied

[I]All five human viral hepatitides have already been reviewed in this series by Drs. Shouval, Gish, Alter, Rizzetto, and Seth and Sherman, respectively.

[¶]The history of these entities and many others have already been published in this series (see essays by Albert Czaja on Autoimmune Hepatitis [Clin Liver Dis (Hoboken) 2020;15(suppl 1):S72-S81] and Paul Adams on Hemochromatosis [Clin Liver Dis (Hoboken) 2020;16(suppl 1):83-90]; others are scheduled to be covered in due course.

on to distinguish among different etiologies of jaundice and other liver afflictions.[74] Yet it must be conceded that, like Voltaire's quip about the Holy Roman Empire,[#] LFTs are neither *liver*-restricted, nor measures of its *function*, nor really *tests* of tolerance or performance[73] (in the sense that a glucose tolerance test assesses glucose handling quantitatively or that creatinine clearance and cardiac output reflect the percent of kidney and heart performance, respectively). Be that as it may, LFTs are widely used to: (1) screen for liver disease, including injury caused by a wide spectrum of medical, surgical, radiological, and radiation interventions, and by medicinal and recreational agents, including herbal and dietary supplements and other complementary and alternative medicines; (2) assess its severity; (3) monitor disease progression; and (4) measure the efficacy of various therapies. Despite the obvious limitations, LFTs are indeed often interpreted as global tests of liver function.

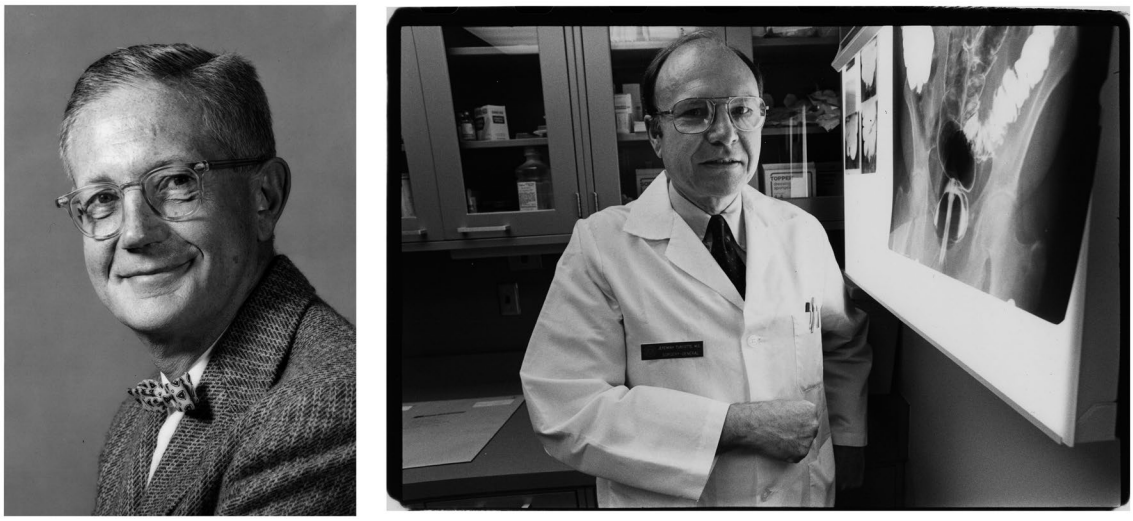
ASSESSMENT OF GLOBAL LIVER FUNCTION

Biochemical tests by themselves or combined with complications of portal hypertension like ascites and encephalopathy have been used to assess global hepatic function. Incorporation of both biochemical and clinical information to determine prognosis was the basis of the Child-Turcotte classification that was developed, using actuarial statistics for the first time in surgical research, by Jeremiah G. Turcotte[76] (1933-2020), who was an instructor in the Department of Surgery chaired by Prof. G.C. Child 3rd (1908-1991) at the University of Michigan (Fig. 13). The Child-Turcotte classification used preoperative serum albumin, serum bilirubin, the severity of ascites and encephalopathy, respectively, and an assessment of nutritional status. Using these variables, patients with cirrhosis who had undergone portosystemic shunting under Child's care were designated as class A, B, or C[75] (according to a liver disease stratification scheme published 3 years previously by Wantz and Payne[77]); patient survival was compared among these three classes.[76]

Child-Turcotte class A patients were determined to be the best surgical candidates. With time, unfortunately, the designation often came to be abbreviated as the "Child Class," as Turcotte's name was rather unceremoniously dropped. In a follow-up study published by Pugh, a medical resident, and others from the late Roger Williams's group in the United Kingdom,[46] nutritional status was thought to be difficult to define and was replaced by the prothrombin time (and later the international normalized ratio [INR]); the ensuing Child-Turcotte-Pugh** (CTP) clas-

[#]In his 1756 Essay on Customs (*Essai sur les mœurs et l'esprit des nations*; Fig. 12), Voltaire (the nom de plume of François-Marie Arouet, 1694-1778; Fig. 12) joked sarcastically of the Holy Roman Empire, that "It was…*ni saint, ni romain, ni empire*" (neither Holy, nor Roman, nor an Empire).[75]

**All too often, the score or class is known as Child-Pugh, once again denying Turcotte his eponymous due.



A CG Child 3rd (1908-1991) **B** JG Turcotte (1933-2020)

FIG 13 (A) C.G. Child 3rd. HS1015, Medical School (University of Michigan) records, Bentley Historical Library, University of Michigan. Reproduced with permission. (B) J.G. Turcotte. HS9059. Photo by Peter Yates, News and Information Services (University of Michigan) Faculty and Staff Files, Bentley Historical Library, University of Michigan. CC BY 4.0.

TABLE 1. CTP CLASSIFICATION: GRADING THE SEVERITY OF LIVER DISEASE[46,77]

Biochemical and Clinical Variables*			
Total bilirubin, mg/dL	1-2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time, seconds	1-4	4-6	>6
Ascites	Absent	Slight	Moderate
Encephalopathy grade	None	1 and 2	3 and 4
Points	+1	+2	+3

*The values in the columns show increasing levels of severity of each of the variables, which were stratified arbitrarily by the authors of references 46 and 77.

sification became the standard to determine operative risk for portosystemic shunt surgery. Scores of 1 to 3 were assigned to the values of the five individual variables, namely, prothrombin time (or INR), bilirubin, albumin, ascites, and hepatic encephalopathy, and the sum of the five individual scores was then used to *score* the severity of liver disease (Table 1). Patients with scores of 5 to 6 points were classified as CTP class A, 7 to 9 points as CTP class B, and 10 to 15 points as CTP class C.

Transjugular intrahepatic portosystemic shunts (TIPSs) were described in 1989[78] and started becoming widely used in the 1990s, but some patients were at high risk for procedure-related mortality. Similar to the development of the CTP score and using data from four centers in the United States, investigators at the Mayo Clinic developed a prognostic model to predict survival after TIPS.[79] The variables in the model were the serum total bilirubin, INR (for prothrombin time), serum creatinine, and etiology of liver disease. Later this model was also found to predict survival among patients with cirrhosis not undergoing TIPS.[79] The model, originally termed the Mayo End-Stage Liver Disease Model (MELD), was validated in hospitalized patients with cirrhosis and ambulatory patients with cirrhosis of varying etiologies, including primary biliary cirrhosis, as it was then known; it was independently validated in an inception cohort of patients with cirrhosis in Italy.[80] Although developed as a prognostic tool to determine mortality risk after TIPS, the MELD score received widest recognition as a tool to prioritize organ allocation for liver transplantation.

Organ allocation for liver transplant in the United States was prioritized in the 1990s largely on waiting time on the transplant waiting list. Patients with ALF received the highest priority (Status 1). Patients with CTP scores ≥10 were assigned to Status 2, and the rest of patients to Status 3. Patients in the intensive care unit (ICU) were subclassified as Status 2A, and the rest of the patients in Status 2 as Status 2B. There were two downsides to this approach. The first was that patients were sometimes admitted to the ICU even if they were ambulatory outpatients *solely* so that they could receive an early transplant. The second anomaly was that for the large number of Status 3 patients, time on the waiting list became the deciding factor for who would receive a transplant. Moreover, among the variables in the CTP score, determining severity of ascites and hepatic encephalopathy was subjective, and the prothrombin time (INR) can vary between laboratories depending on the sensitivity of the thromboplastin used in the assay.[81] Recognizing the problems in the then prevailing system for organ allocation for liver transplants, the Department of Health and Human Services in the United States came up with the "Final Rule" in 1998,[82] namely, that prioritization for liver transplantation should be based on objective criteria and waiting time should be de-emphasized. It was considered then that the MELD would be the prognostic tool to prioritize organ allocation because it was based purely on easily measured objective criteria and had a range of scores wide enough apart that waiting time could be de-emphasized. MELD was subsequently termed "Model for End-Stage Liver Disease," delinking the institution from the score for wider acceptability. Etiology of liver disease was also dropped to avoid misclassification when the etiology was unclear. In February 1992, the MELD score was established as the tool to prioritize organs for liver transplantation. Benefits of this change included reduction in mortality on the waiting list, higher numbers of patients being transplanted, a reduction in the number of patients admitted to the ICU before transplant, and ethnic minority patients no longer being disadvantaged. The MELD score, as shown in Table 2, has subsequently been shown to be predictive of mortality in ALF,[83] alcoholic hepatitis,[84] drug-induced liver injury,[85] and patients

TABLE 2. MELD[80] AND MELD-NA[87] SCORES

MELD Score Calculations
Biochemical variables
Total bilirubin
INR
Creatinine
Sodium
MELD score: $3.8 \times \log_e$ (bilirubin mg/dL) + $11.2 \times \log_e$ (INR) + $9.6 \times \log_e$ (creatinine mg/dL) + 6.4
MELD-Na modification: (0.025 × MELD × [140 – Na]), where Sodium is limited in a range of 125-140, and if outside of these bounds, is set to the nearest limit.

with cirrhosis undergoing surgery.[86] However, over the years since its introduction in the United States for prioritizing patients on the liver transplant waitlist, a number of modifications have been proposed,[87] such as the MELD-sodium (MELD-Na) that is used to adjust the score in transplant candidates with significant hyponatremia.

DYNAMIC TESTS

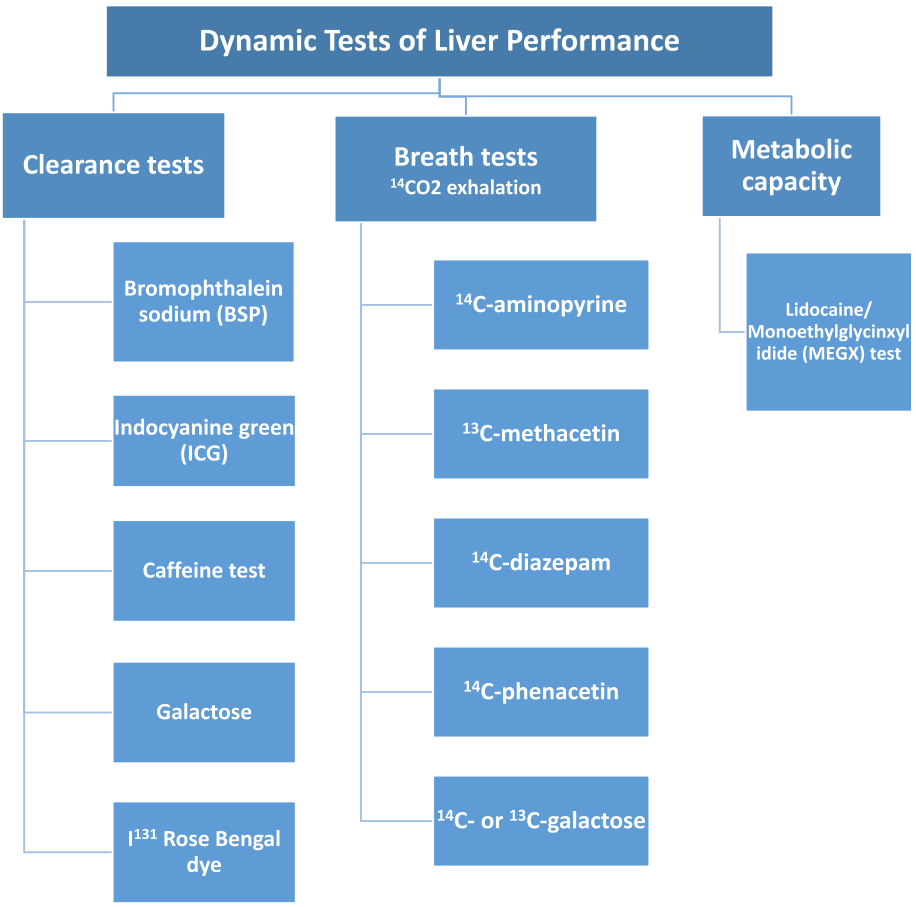
The classic tests of hepatic clearance, also called "dynamic tests," are rarely used nowadays (Fig. 14). These tests were initially used in the assessment of residual liver function in hospitalized patients with shock requiring vasopressors for hemodynamic support, patients with sepsis, and patients undergoing liver resection or awaiting liver transplantation.[88,89] These tests reflect the liver's ability to clear endogenous or exogenous substances from the circulation, a function known as hepatic clearance. The key determinants are organ perfusion and the functional unit of the hepatocytes.[90,91] To measure hepatic clearance, the compound used should have the liver as the sole route of departure from the plasma, and if there are other routes, they should be negligible. The compound should remain in the plasma before extraction by the liver, and equilibrium should be rapidly established if other fluid compartments are used. In addition, clearance should be independent of the concentration of plasma.[91] Examples of dyes used in clearance tests include sulphobromophthalein (also known as BSP) in 1913 and ICG in 1957. BSP binds to plasma proteins until it is excreted by the liver, and therefore the test results can be affected by abnormal concentrations of plasma albumin or by disturbed hepatic blood flow. ICG has a more predictable distribution volume because it is avidly bound to plasma proteins, which helps it measure the blood flow. The plasma level of ICG reflects hepatic uptake because there is low nonhepatic removal, along with great hepatic clearance.[89-91]

In addition, the liver's capacity to transport organic anions as suggested by measurement of serum levels of bilirubin and bile acids, or to metabolize drugs and exogenous compounds (such as lidocaine metabolite formation or breath tests with $^{14}CO_2/^{13}CO_2$ exhalation) can help determine its function.[89-91] These tests may allow assessment of liver functionality and guide the management strategy and treatment response,[92] but they are not helpful when screening for liver disease, are difficult and expensive to perform, and therefore have all but completely fallen out of routine use. However, newer high-tech stable-isotope versions of some breath tests, which are semiautomated and simple to administer and assay, are showing great promise. Table 3 describes some of the older dynamic liver tests. Other research projects investigating liver function assessment include the HepQuant SHUNT test[93] and hepatobiliary scintigraphy[94] (and signal intensity on gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid–enhanced magnetic resonance imaging during the interstitial and hepatobiliary phases.[95] Finally, mention must be made of a simple but powerful test that is being used increasingly in clinical hepatology, one that predicts well the outcome of various complications and therapies of cirrhosis, that is, the measurement of the hepatic venous pressure gradient (HVPG),[96] which incidentally also provides the opportunity to perform a transvenous liver biopsy. The pathophysiological underpinning of the HVPG is, in a sense, arguably one of the most vital of the liver's functions, which so many of the histories retold in this essay embody: normal blood flow through the liver. Unfortunately, HVPG measurement is invasive and requires fastidious technique.[97] In this context, it is to be hoped that the results of comparing HVPG with the ^{13}C-methacetin breath test,[98,99] or indeed any of the other noninvasive dynamic tests currently available (including various elastography modalities[100]), will be successful, allowing for the simultaneous evaluation of liver performance and portal hypertension, and thereby eradicating a duality of endothermic feathered vertebrates using a singular particle of a naturally occurring crystalline composite.

SUMMARY

In summary, liver performance assessment requires a noninvasive test that is well tolerated, reproducible, operator independent, able to assess early and late stages of liver disease, is possibly linked to its pathogenesis, and predicts outcomes. To date, there is an unmet need in hepatology for such a noninvasive test of dynamic liver performance, but, fortunately, there are now admirable candidates for this role. Until the ideal noninvasive tests for assessing both liver performance and the natural history and treatment of disease and treatments materialize, it should not be overlooked that prognostic indices, however imperfect, already exist for these same almost all acute and chronic liver diseases, such as ALF, alcoholic hepatitis, autoimmune hepatitis, causality of

A



B

Function Measured	Test	Principle of Test
Microsomal hepatic function	Breath tests (C-labeled aminopyrine, methacetin, caffeine) Clearance tests (antipyrine, caffeine, lidocaine)	Breath tests are used to probe hepatic microsomal P450 enzyme activity and investigate hepatocellular function by assessing liver oxidation. The exhaled labeled CO2 is measured. Clearance tests probe the hepatic microsomal P450 enzyme activity and measure either the metabolic elimination of the test compound or the appearance of metabolites in the blood that are primarily dependent on the hepatic metabolic capacity.
Cytosolic hepatic function	Elimination capacity test (galactose)	The capacity for elimination of galactose is estimated by serial measurements of serum galactose levels after administration of an intravenous bolus of galactose; galactose is metabolized by the cytosolic enzyme galactokinase.
Liver perfusion and Biliary excretion	Clearance test (indocyanine green)	Indocyanine green is distributed in the serum, removed by the liver, and excreted unchanged into bile without entering the enterohepatic circulation.
Liver perfusion	Clearance tests (low-dose galactose, sorbitol)	The high rate of hepatic extraction of low-dose galactose and sorbitol by the sinusoidal membrane of hepatocytes implies a hepatic plasma flow–dependent mechanism.
Hepatocyte mass	Uptake test (technetium-99m– Galactosyl human serum albumin labeling)	Technetium-99m–galactosyl human serum albumin accumulates only in the liver by ligand–receptor binding and is visualized on scintigraphy.

FIG 14 (A) Dynamic tests of liver performance. (B) Examples of a few dynamic tests that were studied to assess the liver function preoperatively, showing the function measured and the principle of the test. Table reproduced with permission from *New England Journal of Medicine*.[89] Copyright 2007, Massachusetts Medical Society.

drug-induced liver injury, and complications of cirrhosis, and therapies such as liver transplantation, relief of Budd-Chiari syndrome, and many others. Many of these indices can be calculated easily nowadays on handheld and desktop devices with the aid of individual applications ("apps") that have been developed by investigators

TABLE 3. EXAMPLES OF DYNAMIC TESTS OF LIVER PERFORMANCE[88,89]

Test	Description
Clearance tests	
Sulphobromophthalein (or BSP)	- First used in 1913 - Indication: a ssessment of dynamic liver function - Water soluble - Binds to plasma proteins - Conjugates with glutathione before excretion in bile Summary of the test: - IV injection of BSP - Complete extraction by the liver - In normal individual: <10% remains in the serum by 30 minutes and less than 5% by 45 minutes - Extraction and removal by the liver is related to hepatic blood flow and canalicular bile transporter protein function Clinical application: - Slower rates of extraction are seen in liver disease - In patients undergoing liver resection, a negative prognosis can be predicted by increased retention after 15 minutes - Can differentiate between Dubin-Johnson syndrome and Rotor syndrome
ICG	- It was recommended to assess hepatic blood flow in 1957 - Indication: a ssessment of dynamic liver function - Excretion of ICG exclusively into bile - Does not undergo intrahepatic recirculation - Appears in bile acids within 8 minutes of IV infusion Summary of the test: - A transcutaneous system is used to assess the clearance rate and plasma disappearance rate noninvasively - In normal individuals: the clearance rate of ICG is >700 mL/min/m^2, and its plasma disappearance rate is >18%/min Clinical application: - Decreased rate of plasma disappearance in liver disease - Prognosticate patients undergoing liver resection - Evaluation of the liver function of potential live donors
Caffeine test	Useful in severe liver lesions Correlates with BSP and the $^{14}CO_2$ breath elimination test Mechanism: quantifies hepatic microsomal activity Summary of test: - Caffeine is administered orally - Dose = 300 mg - Quantification of caffeine and caffeine metabolite levels in the blood Clinical application: - Caffeine elimination rates are increased in cirrhosis - Lower caffeine metabolite/caffeine ratio in cirrhosis
Breath tests	
^{14}C-Aminopyrine test	- Most common - Correlates with the degree of liver damage - Radiolabeled aminopyrine is ingested orally - Aminopyrine undergoes demethylation in the liver - Microsomal liver function can be assessed based on exhaled $^{14}CO_2$ Clinical application: - Prognostication of patients with chronic liver disease
Metabolic capacity	
Monoethylglycineexylilide (MEGX) test	- This test is based on the hepatic conversion of lidocaine to MEGX - Conversion is related to the cytochrome P450 system - Use of this test is limited by the need for laboratory equipment/immunoassay - Can be influenced by patient-related factors, as well as hepatic metabolic capacity and blood flow - Consider interactions with substances or drugs that result from the cytochrome CYP3A/4A system Clinical application: - Quantitative assessment of pretransplant and posttransplant liver function
Tests rarely performed in clinical practice	
Amino acid clearance test	Evaluate periodic plasma clearance of amino acids after standardized infusion dose.
Galactose elimination capacity	- Used early in the clinical course of jaundice - Distinguishes between hepatocellular disease and biliary obstruction - Assesses the liver's capacity to convert galactose to its phosphorylated form: galalactose-1-phosphate - Clinical value is limited, especially because of galactose intolerance

in their respective fields (e.g., for MELD, Transplant-Free Survival from ALF, etc.) or using collections of apps, such as HelpCalc (available from the App Store), which was created and especially designed for hepatology by Dr. Gary Poleynard, with some assistance from Michael Davies.

SERIES EDITOR'S POSTSCRIPT

The current essay by Drs. Mousa and Kamath is by far the longest yet in the History of Hepatology series, and rightly so. Whereas other authors in this series have elegantly and informatively reviewed the history of the respective chosen topics of their expertise, in this essay, the authors from WFMC (The World-Famous Mayo Clinic) have provided a long-overdue overview of the history of liver studies as a fitting backdrop to efforts made over the centuries to assess the performance of the liver. In antiquity, the liver was used to predict the future, but then the impetus quickly changed to devising means to predict the future of the liver disease and its impact on the owner of that diseased organ. Hepatologists are at a disadvantage compared with their pulmonary, cardiology, and nephrology colleagues, because the functions of their organs of interest, so to say, are monothematic. A simple alliterative mnemonic sums up the global function of the lungs, heart, and kidneys—the lungs Puff, the heart Pumps, and the kidneys Pee. The liver has no such unitary global function; therefore, there cannot be a global LFT. Instead, we have a battery of tests related to the different functions of the liver—catabolic, anabolic, excretory, secretory, detoxifying, etc.—as well as measures of liver performance that predict outcomes, which are summarized here. Incidentally, it is probably a forlorn hope that the time-honored but specious term *liver function tests* will ever be expunged from the hepatological dictionary, as it trips easily off the tongue even though it erroneously seems meaningful.

In the context of the purpose of the present essay, who better could be charged with the responsibility of describing the evolution of liver function assessment than the senior author Patrick Kamath—who devised an innovative simple arithmetic index of liver performance with global impact (calculated from readily available serum variables), namely, the MELD score—and his junior colleague Omar Mousa. In addition to his clinical practice and clinical research achievements, Patrick is a legendary teacher, for which he has been repeatedly recognized and honored by the Mayo Clinic College of Medicine (upward of a dozen times), the Mayo Clinic Foundation, and the American Gastroenterology Association, culminating in the presentation of the Distinguished Clinician Education/Mentor Award of the American Association for the Study of Liver Diseases in 2018. The readers of the current series are fortunate to have access to the mentorship embodied in this essay.

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